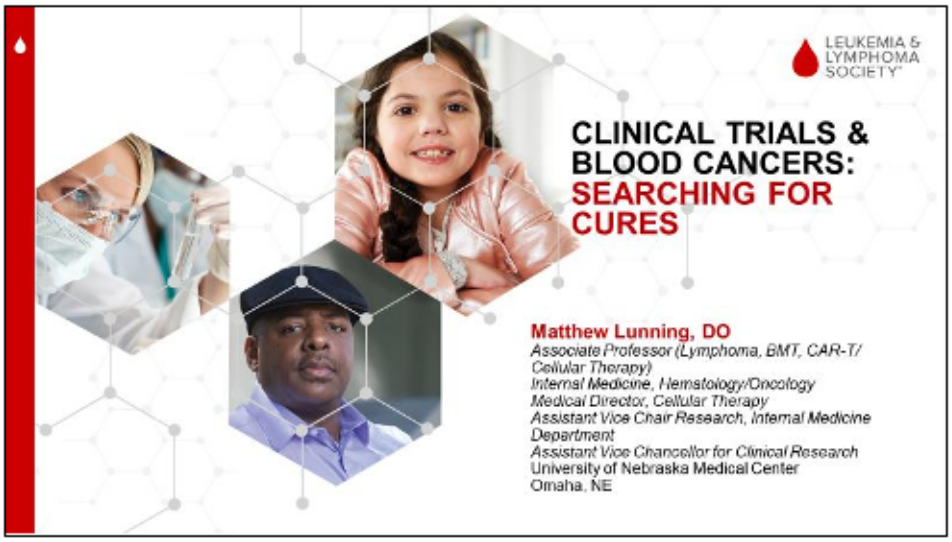
WELCOME AND INTRODUCTION



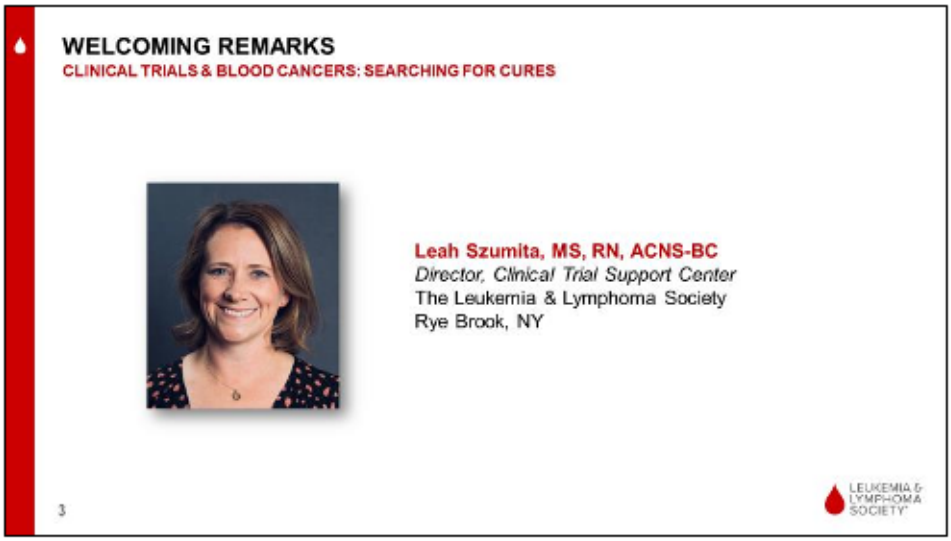
Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you.

Special thanks to Dr. Matthew Lunning for volunteering his time and expertise with us today. We have over 2,500 people participating in today's program from across the United States as well as other countries, including Australia, England, Canada, India, Ireland, Italy, Pakistan, Romania, Tunisia, the United Kingdom, and Yemen. We are also taping and transcribing this presentation.

The Leukemia & Lymphoma Society funds leading edge research for every type of blood cancer. As the largest nonprofit funder of cutting-edge blood cancer research to advance cures, LLS has invested more than $1.6 billion in cancer research since we started in 1949, leading to breakthroughs in immunotherapy, genomics, and personalized medicine that are improving and saving the lives of patients.

Thank you for joining us for this important update on clinical trials in blood cancers. In the future, please continue to inform us of what information you need, and please continue to let us be here for you.



Before we begin Leah Szumita, our Director of our Clinical Trial Support Center, will make some opening remarks.

Leah Sumita MS, RN, ACNS-BC

Hello, my name is Leah Szumita; and I am the Director of the Clinical Trial Support Center (CTSC) at LLS. We know that trying to find a clinical trial can be overwhelming. Fortunately, The Leukemia & Lymphoma Society provides a free service to help. The Clinical Trial Support Center is a team of 11 nurse navigators with expertise in pediatric and adult blood cancer who help patients, their families, and healthcare providers identify potential clinical trials and overcome the barriers to enrollment. A designated nurse navigator will work one on one with you to learn more about your unique situation, provide education about different treatment options, including clinical trials, identify support resources, and work together with your healthcare team to help you access the treatment that is right for you. Your nurse navigator will guide you in your efforts to enroll in a trial and be available for support throughout your entire clinical trial experience. If you or a loved one are interested in learning more about clinical trials as a potential treatment option and to connect with a nurse navigator, please call the Information Resource Center at 1-800-955-4572 or go to our webpage at www.LLS.org/CTSC.

Lizette Figueroa-Rivera, MA

Thank you, Leah. Again, Leah and her team of nurse navigators are available to speak to you more about clinical trials and will assist you throughout the entire process.

PRESENTATION

Lizette Figueroa-Rivera, MA

I am now pleased to introduce Dr. Matthew Lunning, Associate Professor in the Division of Hematology/Oncology at the University of Nebraska Medical Center. He also serves the Department of Internal Medicine as the Associate Vice Chair Research, Assistant Vice Chancellor for Clinical Research, Medical Director of the Clinical Research Center, Medical Director of Cellular Therapy and Medical Director of Lymphoma Research.

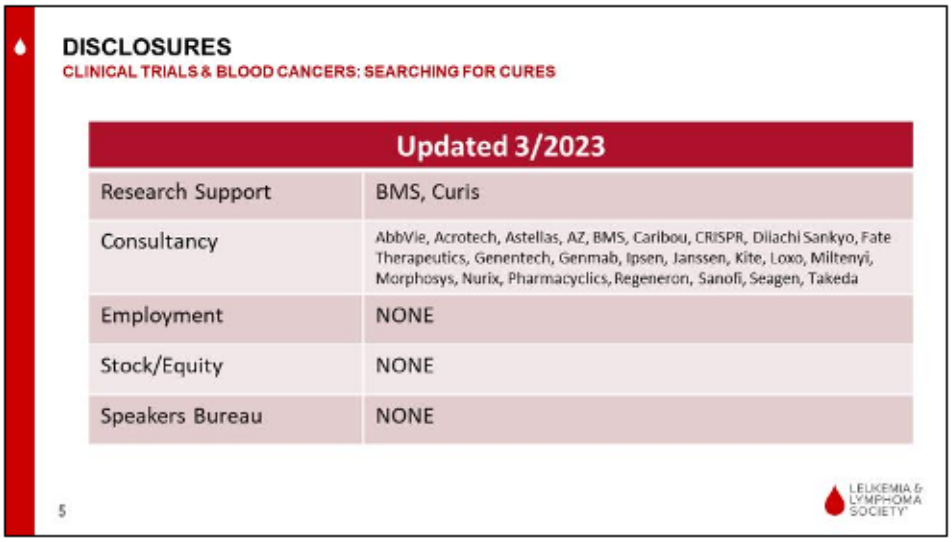
Dr. Lunning, I am now privileged to turn the program over to you.

Matthew Lunning, DO

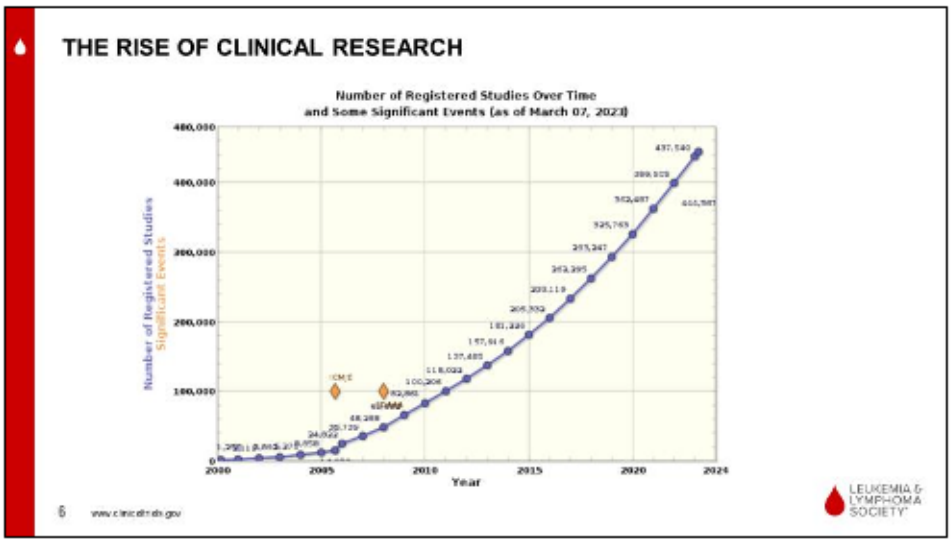
Thank you very much and thank you all for attending. I guess this is a global audience. I can say good morning, good afternoon, good evening; and if you're waking up in the middle of the night, I hope you quickly can get back to sleep after you hear this presentation and hopefully get your questions answered.

I think what I was most excited about when I got the invitation was the opportunity to engage with individuals across the world who have questions about clinical trials and how we can, as investigators, and how we are trying to improve the outcomes for patients with blood cancers.

As you can see here, I take care of patients with lymphoma. I also do bone marrow transplants as well as CAR T (chimeric antigen receptor T cells) and other cellular therapies. I wear a couple of different hats at the University of Nebraska Medical Center in regard to clinical trial operations, as well as kind of have my boots on the ground as a principal investigator of clinical trials but also trying to improve the speed at which we can do clinical trials at our institution.

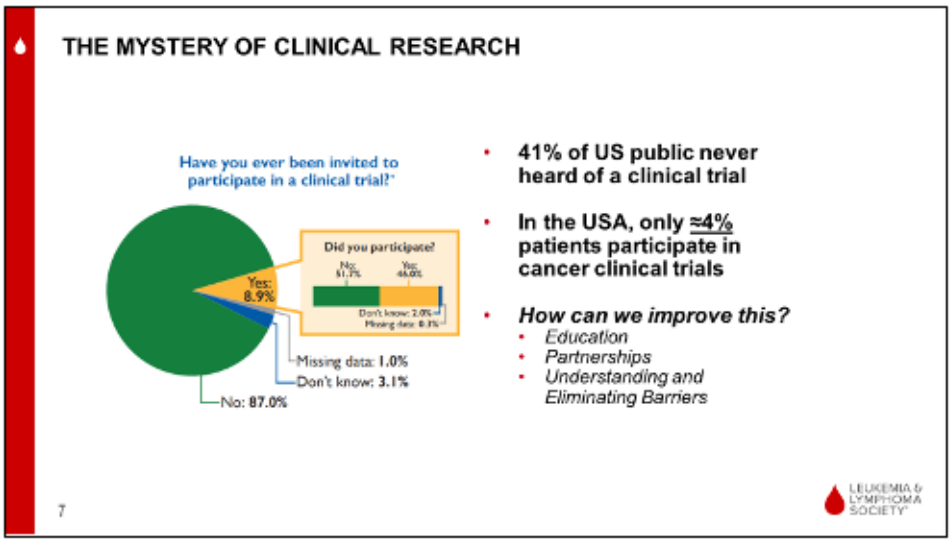


And here are my disclosures that are up to date through this month.



So, one would think that in the midst of the COVID (coronavirus disease 2019) pandemic that clinical research slowed down in oncology, and I think that that is one of the misperceptions. Maybe clinical trials did change a little bit during the COVID pandemic, but here you can see kind of over time the trajectory of registered studies. Some of these do include oncology studies, but in oncology we may have slowed down clinical research during the pandemic, but it is certainly picking back up.

One of the issues with regard to clinical trials currently that many institutions as well as many businesses are having is just workforce issues. And so, we've really had to think differently about how we do clinical research in 2023 and beyond, and we'll kind of talk about how we do clinical trials differently post or in the midst of the pandemic in oncology; but we didn't necessarily stop because we knew that cancer still needed to be treated. Now we did kind of divert some of our resources to really bolster up, for instance, vaccine research; but those research studies have now ended, and clinical research is strong, and it is increasing.



One of the things about a mystery of clinical research is part of the what's out there and what people have ever been exposed to clinical research. And I found this very interesting pie chart here with the question of have you ever been invited to participate in clinical research? And usually green means yes, but in this pie chart no was green with 87% of individuals, so 87 out of 100 individuals, if they've ever been asked to participate in a clinical trial, the answer was no.

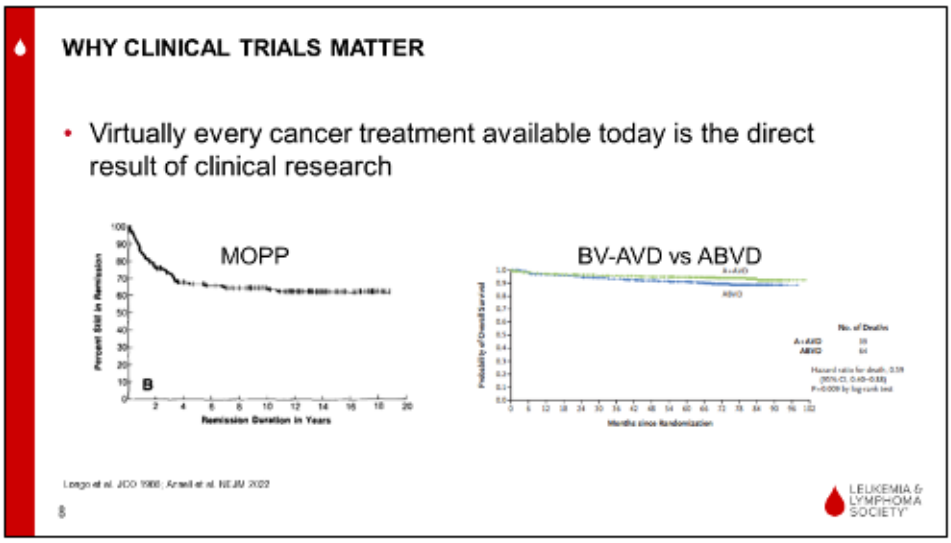
But let's look at that yellow piece of the pie, so that 8.9% of the people that were approached to participate in a clinical trial, and if you dive in a little bit deeper into those individuals, and again this is all-comers to clinical research, 51.7% of them said no to participate and 46% said yes. So, about a 50/50 chance if you approach somebody to participate, they will be interested in potentially participating in clinical research.

If you look specifically into the United States, about 41% of the US (United States) public has never heard of a clinical trial. And if you dive down deeper into cancer clinical trials in the United States, only about 4% of patients participate in cancer-related clinical trials. Now, this is a very low number comparatively, I think, to other countries; and how can we improve this?

Why, I think the first part is with education, about what clinical trials really are, and programs like this are the start and the continuation of that education. We need partnerships between investigators, clinicians, care teams, organizations like The Leukemia & Lymphoma Society to get out the message of just how important clinical research is to moving the needle and moving the outcomes to

betterment of care for patients with all cancers, all clinical conditions, and specifically here today, blood cancers.

A lot of this comes with understanding and eliminating barriers. We've heard a lot about what barriers may exist in clinical research. I highlighted a couple of those. Even though clinical trial access may be increasing in regard to the number of trials, if you don't have the bodies or the people to conduct that clinical research, it can be very taxing to those who are trying to do it. We also need to be mindful that when we do clinical trials we want the clinical trials to be representative of the population that it serves, not only in the state or the county or the city but the country or, as we are in a global environment here today, that we want to best serve the global community in regard to cancer research and blood cancer research.



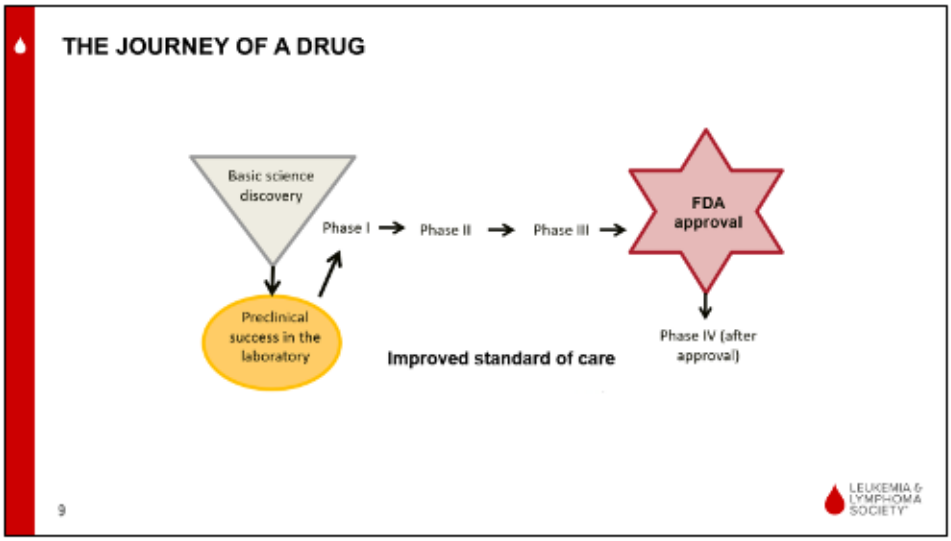
So, why does clinical trials matter? Well, virtually every cancer treatment available today is a direct result of clinical research. Even if you rewind and hop in your DeLorean and go back to the 70s and 80s, clinical research was being done to advance cancer care. And I'm giving a story here with two different curves, okay, highlighting a blood cancer called Hodgkin's lymphoma; and Hodgkin's lymphoma was our first lymphoma identified, and that's why it's Hodgkin's lymphoma, and everything thereafter became non-Hodgkin's lymphoma.

And as you can see here, to the left is a chemotherapy regimen called MOPP was one of the first chemotherapy combination regimens after radiotherapy for the treatment of Hodgkin's lymphoma that had shown, and this is showing over 20 years of follow-up to individuals who received MOPP, and you can see there's a plateau on that curve. Okay, and some of these chemotherapies started off as individual chemotherapies that were then felt to potentially be, have nonoverlapping toxicities; and they work together to cure Hodgkin's lymphoma.

You can see about 40 to 50 years later now a clinical trial, which was a randomized, Phase III clinical trial of brentuximab vedotin versus combination AVD versus ABVD in advanced stage Hodgkin's lymphoma recently was published to show an overall survival advantage with BV-AVD in advanced

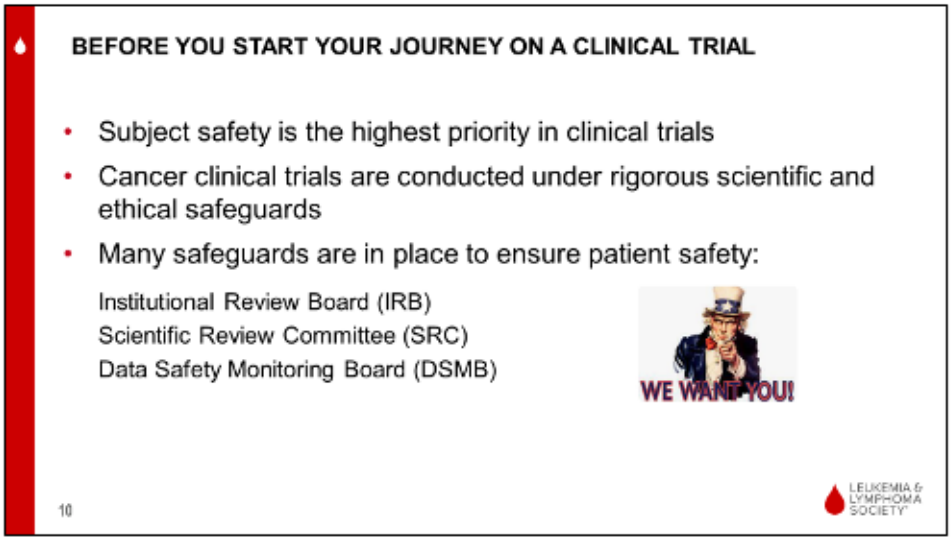
stage Hodgkin's lymphoma versus ABVD. ABVD had been one of the standards of care for many decades in Hodgkin's lymphoma, and only through a global effort could this randomized clinical trial in Hodgkin's lymphoma be done.

And you can see here with the curves on the Y axis or the left side vertical axis just showing that we have improved the outcomes from MOPP all the way to BV-AVD and ABVD over time, and we've done that through numerous clinical trials informing the care of this one lymphoma; but we've also had many examples of where clinical research has brought forward curative intent therapies in non-Hodgkin's and Hodgkin's lymphoma as well as other hematologic malignancies.



So, if we talk about trials, we're often talking about a drug or drugs in combination. And so, where does this kind of start, and what is often the end to get the drug or the drugs, that is in a combination, out into the commercial environment where more than just off of a clinical trial can that drug or combination be utilized.

So, many times, you can see here in the gray triangle, a lot of drugs start off in drug discovery labs as basic science projects. They are then tested in preclinical models in the laboratory to demonstrate that these agents have activity, whether or not they can slow down cell division or actually take out or kill the cell through several safety steps before in the preclinical environment. The study or the study drug then enters into the study realm where it is in a Phase I and then progresses to Phase II and then Phase III and then often the United States Food and Drug Administration (FDA) approvals. So, FDA is applicable to those drugs going through approval in the United States. However, many countries have their own approval bodies. And some, like in Europe, may use a consort or a group of countries may come together with one approval body. After a drug is approved, then Phase IV studies are typically what we call postmarketing or after-approval studies.



So, before you start your journey on a clinical trial, I think that there are some ground rules before Uncle Sam, you know, which is often where we may recruit, or you may see flyers or you may hear about opportunities for clinical trials, but we want you to know that subject safety is the highest priority in clinical trials. Cancer clinical trials are conducted under rigorous scientific and ethical safeguards, and many of these safeguards are in place to ensure patient or subject safety. I've listed just three here that I've either participated on or sent studies through.

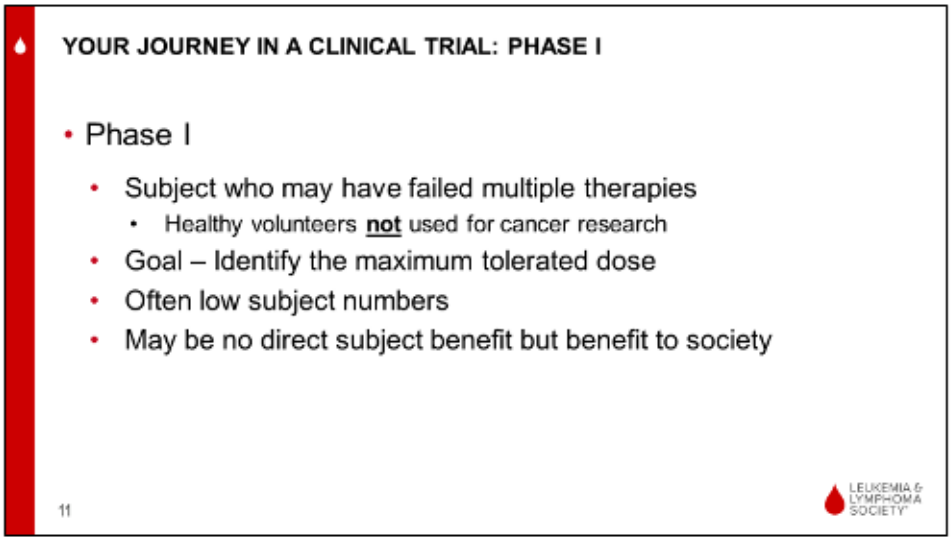
So, the first one is an institutional review board, so this is a group of individuals that may be clinicians, pharmacists, nurses, advanced practice providers, and even the lay public sit in a board that reviews informed consent forms that prior to subjects being offered clinical research that talks about the risks and the benefits. Also, you know, what is the schedule of events? What are the procedures that would be done, and what are the risks of those procedures on a clinical trial?

And really these informed consents are supposed to be at an eighth grade reading level or below, such that when it is produced to a potential subject, that and with an opportunity for questions and answers, that these informed consent forms are readable, understandable, and actually questions can be derived after reading these informed consents such that you can sit down with your care team and ask meaningful questions about how this clinical research may be relevant to your disease, relative to where your disease is at, and how it may be impactful to your life, and what are the alternatives to the clinical trial?

A scientific review committee or an SRC committee reviews the science of the clinical trials, and many, if not all, cancer clinical trials will receive scientific review. This is basically looking at the merit and making sure that the clinical trial has the scientific merit to proceed on.

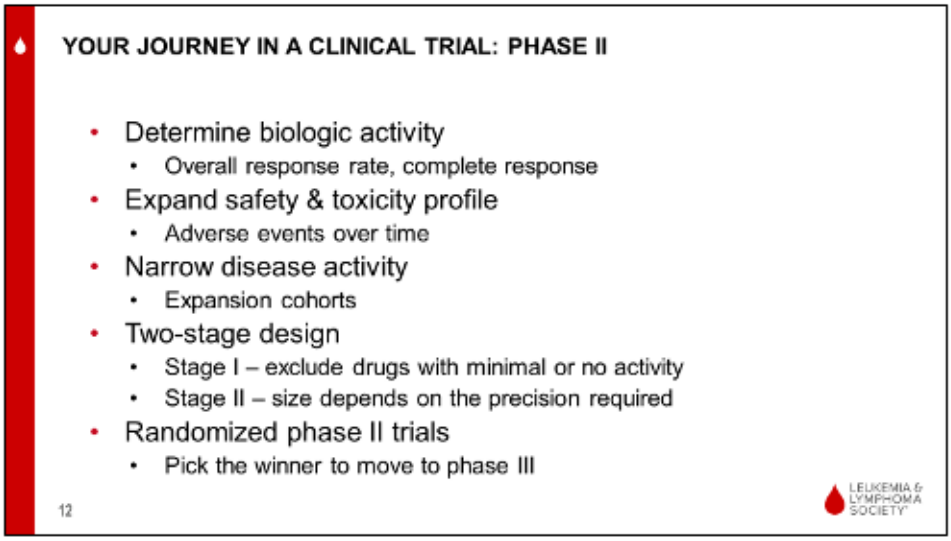
And the Data Safety Monitoring Boards are those boards that live in the shadows of the clinical trials often and are analyzing for adverse events of significant interest or what we call significant, unanticipated adverse events. They will also review kind of the percentages, the degree, whether or not it was felt to be related to or not related to the clinical trial or the study drug. And so, these boards

will often state whether or not it is safe at different periods of the clinical trial, if it is safe for the clinical research to continue to move on. So, a lot of safeguards that are either before a clinical trial is even activated at a specific site or safeguards that continue to be ongoing while a clinical trial is being conducted.



So, let's dive a little bit deeper into different phases of clinical trials; and so, the first phase that I referenced, once a drug goes from the bench to the bedside is a Phase I clinical trial. Commonly, Phase I clinical trials are for subjects who have failed multiple therapies. I will say all of these are not rules. They're just caveats. Okay, and so I can show you Phase I trials where it may be in the frontline of clinical trials in untreated patient populations.
Typically in cancer research, healthy volunteers are not used for Phase I clinical trials. The goal of many Phase I clinical trials is to identify what's called the maximum-tolerated dose. And so with that, in the trial design, we identify characteristics that would meet a dose-limiting toxicity. So, a dose of a drug and if it met a criterion based upon a dose-limiting toxicity, we will ask ourselves, based upon the number of subjects that have a dose-limited toxicity, whether or not we've reached that maximum tolerated dose. And so, often in Phase I clinical trials we are searching for either the maximum-tolerated dose or that maximum-tolerated dose may not be reached based upon no dose-limiting toxicities. And at that point there's a decision made to move on if an MTD or maximum tolerated dose is not reached.

Often, there are low subject numbers in Phase I's because, again, you're looking often at a toxicity signal rather than an efficacy or how well the drug works signal. And in Phase I studies, there may not be any direct subject benefit, but there will be benefit to society trying to move a clinical compound forward.



In a Phase II clinical trial, often what you're doing here is to determine the biologic activity of that agent or that combination, and so, this simply can be defined as an overall response rate, which in many lymphomas or blood cancers are the, it's an additive percentage of those who achieve a complete response rate; and a partial response rate equals an overall response rate. In other clinical research protocols, you may see different definitions of biologic activity.

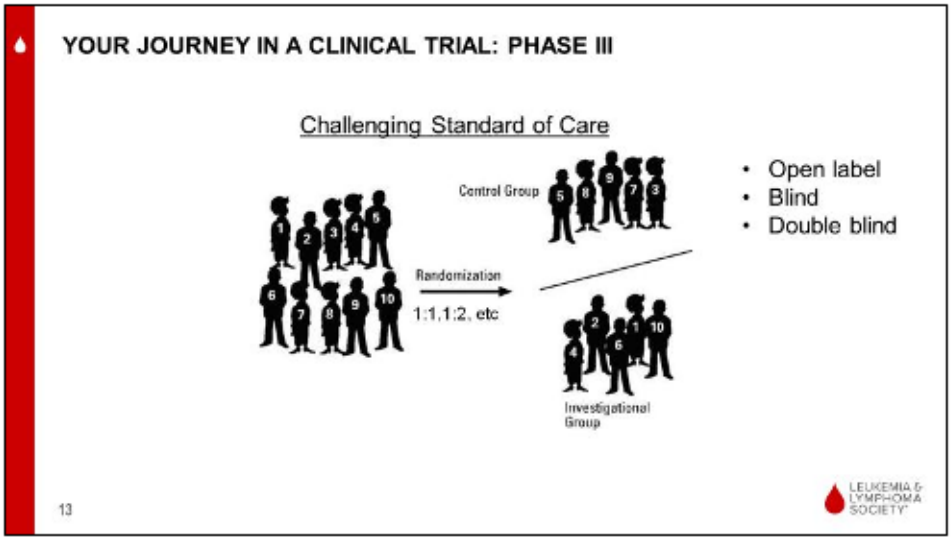
Also with this, you will assess for expanded safety and toxicity profile. In many Phase I trials, the dose-limiting toxicity definitions may have a finite timespan where it is just for cycle one. In Phase II clinical trials, you are digging deeper into subsequent cycles and recording the adverse events that occur over time because it's important as an investigator to know that, well yeah, maybe there isn't significant toxicities or events in the first month, but if we see events that become cumulative over time, we want to know that, understand that because that helps us inform our practice and helps us inform our patients if they were going to go onto a clinical trial.

Furthermore, in Phase II clinical trials, if we're starting to see efficacy in a specific disease, it affords and allows for the opportunity to expand those cohorts. For instance, in non-Hodgkin's lymphoma, there's over 60 different subtypes of non-Hodgkin's lymphoma; and we may see differential activity in some of those subtypes compared to others. And so, in Phase II clinical trials, often we can expand specific cohorts to accrue more subjects to see if that efficacy is real or not.

Sometimes, we will go after what's called a two-stage design where we use an approach where a stage one would exclude drugs with minimal or no activity. And so we say if this drug does not have an X percent response rate within Y number of patients, we will not move it into a broader or a larger sample size. And that sample size, if it's met, moves into a second stage; and that really depends upon the precision of what is required.

So for instance, if you're trying to state, "Well, this is the base response rate of 30%, and if it gets to a response rate of 40% or 45%, then we feel that this is a compound or a combination worth testing further or worth testing in a randomized fashion". And the randomization means like a heads or a tail

on a quarter where some people go to the left and some people go to the right. And in randomized, Phase II clinical trials, really you're looking at trying to pick potentially a winning arm or a winning schedule to move onto a Phase III clinical trial.



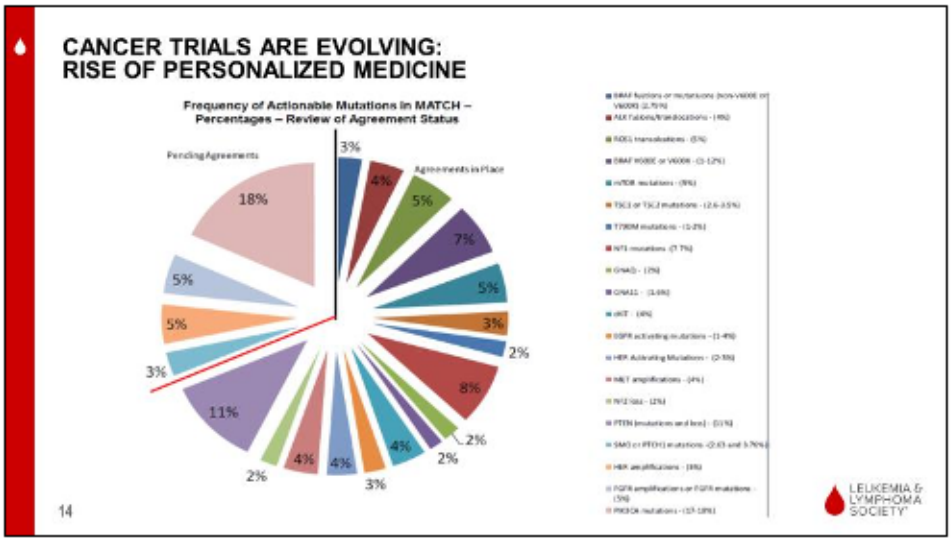
Alright, so many of you may have heard of a Phase III clinical trial because this is often the endpoint of clinical trial research where you have an experimental drug or an experimental combination going up against the standard of care kind of control arm. And in this cartoon to the left, you can see ten potential subjects, and they all would have sort of an eligibility criteria that would have been met so that you're trying to create as homogeneous of a population so that everybody has met these criteria prior to entering into a clinical trial. They are then randomized, and randomization, and this is a two-arm design where you can see there's a control group and investigational group. There can be multiple arms at the time of randomization.

And randomization can be in a one-to-one fashion where it would be one person has equal odds of going to the control group or the investigational group; and other randomizations can be in favor of one arm or the other or in a one-to-two odds design. And so, you would have more people potentially randomized in a two-to-one fashion into the investigational group over the control group.

Phase III clinical trials can be open label. So, open label clinical trials means that you as the patient know what drug you're getting and me as the investigator knows what you are getting. There can be single-blinded trials where you as the subject may not know what drug you're getting and me as the investigator knows or the pharmacist knows. And then really the best clinical trial designs are a double-blind clinical trial where you don't know what drug, if you're getting experimental drug or the investigational drug, and I don't know what you're getting as an investigational drug or the control group.

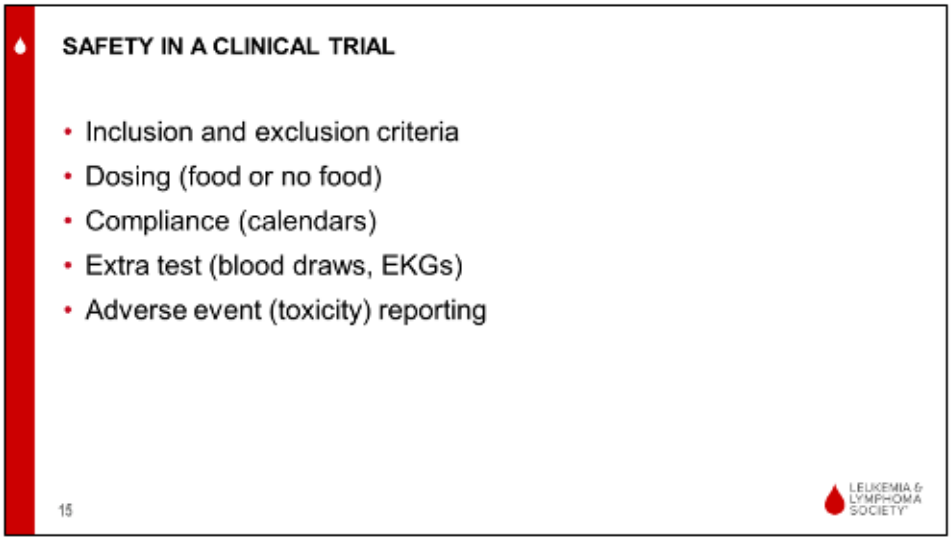
The best example that I can give and most, or not the best example, but an example I can give recently was the POLARIX trial, which was done in advanced stage diffuse large B-cell lymphoma, our most common non-Hodgkin's lymphoma where patients were blinded and investigators were

blinded to whether or not a patient received polatuzumab vedotin or vincristine in combination with a backbone of rituximab, cyclophosphamide, doxorubicin and prednisone. Okay, and so that was a double-blind, randomized trial that was done all over the country; and so, I didn't know, the patient didn't know if they were getting vincristine or if they were getting polatuzumab vedotin. So, that's an example of a double-blind clinical trial.



Now, many clinical trials are, you know, in phases that's very dogmatic. But really we are moving the needle and testing different hypotheses in clinical trials; and they should be evolving as we get better and more knowledge that perhaps it's not necessarily about the disease, but it may be about a marker or a change in the genome or the change in how the genes are turned on and turned off or a genetic signature or target that is amplified, causing a cell to become cancerous. And this is just a pie chart of different mutations that may promote personalized medicine to where that mutation may lead to a therapy given to you based upon that mutation.

Now, this is seen much more play, I think, in non-hematologic malignancies, but we continue to search for personalized medicine in hematologic malignancies certainly; and there are some great examples of personalized medicine based upon different genetic changes. For instance, the initiation in chronic myelogenous leukemia with the tyrosine kinase inhibitors targeting BCR-ABL, and so, that was really a very good personalized and targeted therapy for that disease, which revolutionized the therapy for that disease.



So again, how are we creating safety in clinical trials? I alluded to that there are inclusion and exclusion criteria, so you have to meet certain criteria about your disease, number of prior lines of therapy, what your kidney function is, how your liver function is, what's your blood count, so your hemoglobin and platelets are, and you have to meet a certain threshold in order to be included. And then exclusion criteria may say you may be excluded if you haven't had enough therapies or if you have a concurrent condition that makes the risk outweigh the potential benefits in the eyes of the writers of the clinical trial.

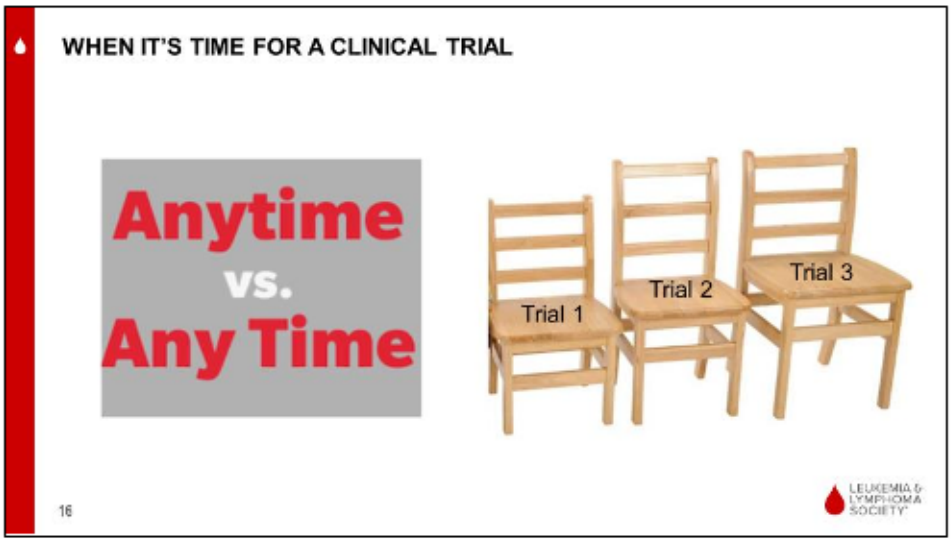
Also within the clinical trial, it's very set on what the dosing of that drug is. It isn't that you're going to get 100 to 200 milligrams of a drug, it would be you're getting 100 milligrams of a drug. And they will tell you it needs to be taken with food or without food or with or without certain medications. So, clinical trials can be and are often very regimented in regard to the dosing and the schedule.

We often want the administration of these drugs or agents to be very specific and to denote significant compliance. And we do this by giving individuals drug calendars so that they note the date and the time that they took their experimental product or their experimental agent.

Through many of the clinical trials, regardless often of phases, there may be extra tests that are necessary that would be done beyond what would be standard clinical care. This could be extra blood draws or extra blood drawn at a time of a standard-of-care blood draw. This also could involve doing electrocardiograms to look at the electricity of the heart, or it may require extra scans, whether or not that's a CT (computerized tomography) scan or a PET (positron emission tomography) scan to check for the efficacy of the study drug or the study combination.

And then at each visit, you're often asked about adverse events. You will often be asked by the team, as well as the investigator, and what happens then is the investigational team adjudicates these adverse events and they're graded, and then they're discussed whether or not they are felt to be related to the study drug or the study combination. And then you make reference back to the protocol on how to proceed, whether or not as holding the therapy, whether or not it is dose-reducing the

therapy, or acknowledging that these adverse events are expected but within safe limits; and you proceed with the therapy.



So, I often get asked this question, when is it time for a clinical trial, and I found this interesting, this anytime versus any time. You know, I wasn't always the best at English when I was growing up in elementary school, but I found out that you can use anytime without a space or any time with a space pretty much anytime.

And so, when I think about clinical trials, you know, I think that you could ask a question; and there may be a clinical trial available at any time point. There could be a clinical trial at the beginning of a timepoint of when you're newly diagnosed and even if you have a lymphoma where it may be recommended that you go under active surveillance. And so, sometimes these can be registry trials, these can be human biologic material trials, there can be quality of life trials, and so not always does it have to be an interventional, meaning you're doing an intervention, asking a question, and a therapeutic, meaning that you're giving a pill, an IV (intravenous). You know, sometimes it can be beyond a therapeutic drug trial.

And I think I used this chair analogy in that trials come in all different shapes and sizes, and when you discuss a trial, you have to really sit down and kind of go back and forth in your chair and side to side to see does this trial feel right for you? And me as an investigator, I'm asking myself is this trial right for this person because you may meet the eligibility, but it's just not the right trial for you at the right time.

And I think one of the most important messages that I can give about clinical trials and the conduct of clinical trials is really the chair must fit. Okay, that it must be the right time for you and your care team to do the clinical trial. It may be three months from now when that chair's going to fit better, if the clinical trial is still open, or it may be now. But I think one of the key importance here is really to take the time to discern and feel out whether or not the clinical trial is right for you.

And then how do you find a clinical trial? Well, I would say that the resources have become so much better about finding access to clinical trials. We heard about the LLS's Clinical Trial Support Center (CTSC), and I think that that is great with their embedded nurse navigators.

There is federally funded, through the US National Library of Medicine a site called *ClinicalTrials.gov*. There's over 215 million pages viewed; 145,000 individuals daily go to this site. It has a smart search just like many other sites do to where you can really cone down or be very specific on this is my type of diagnosis, you know, from that standpoint and what clinical trials may be available.

From a site-specific standpoint, you know, I work at the University of Nebraska Medical Center (UNMC), and we have for our patients or patients that may be coming to us from regions or nationally, they can type in certain key words; and clinical trials that are available as UNMC become available.

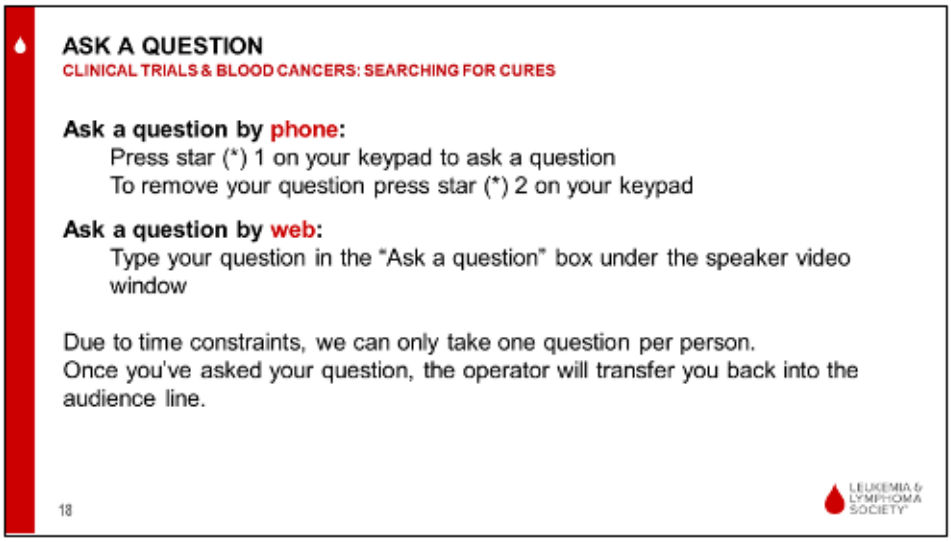
Obviously, The Leukemia & Lymphoma Society has their support center. I have personally received emails from them about somebody who was interested in a clinical trial and trying to match up patients with centers that have potential clinical trials open and perhaps being a conduit to furthering clinical research in hematologic malignancies.

Well, my presentation is over, and I want to thank you all for listening in. But now for my favorite part, which is getting to hear from you and answer some of your questions about hem malignancies or about clinical trial conduct in general; and thank you for your attention.

Lizette Figueroa-Rivera, MA

And thank you so much, Dr. Lunning for volunteering your time with us today and updating us on clinical trials for blood cancers.

QUESTION-AND-ANSWER SESSION



Lizette Figueroa-Rivera, MA

And as you mentioned, it is now time for our Question-and-Answer portion of our program. For everyone's benefit, please keep your questions general without many personal details so Dr. Lunning can provide answers that are more general in nature.

Now for treatment questions that do not address clinical trials, we do encourage you to speak to your treatment team to get a more personalized and detailed answer.

Thank you, and we'll take the first question from our Web audience. Doctor, we have many people asking about age when it comes to clinical trials. Judy's asking, "Are clinical trials targeted to younger patients?"

Matthew Lunning, DO

Not necessarily. I've been a big proponent of trying to really understand why, if an upper age limit is in a trial, that it's justified. I think that we can provide examples, and I'll provide one right now where in CAR T-cell therapy and our aggressive lymphomas, we've shown over time and within clinical trials and the real-world experience that patients over the age of 65 are doing just as well as patients under the age of 65.

Now when you go down to the lower age limits, some states define when an adult is as 18. In my state of Nebraska, the age is 19. There is now a movement for young adult clinical trials where you are breaking down this barrier of what's called AYA (adolescent and young adult), so up to the age I believe of 25 and down, many trials down to the age of 12. But when you go into pediatric oncology, sometimes the regimens change, how doses are delivered changes, and so the lower limit may be just purely based upon how therapies were developed. I would say that our Children's Oncology

Group has done an absolutely excellent job of pushing the envelope, and there are many investigators who are now pushing that envelope too in the AYA population to bring homogeneity and bring clinical trials to not only our pediatric patients but our young adult patients. I really think that we should be opening up and not using age many times as a prerequisite to clinical trials.

Lizette Figueroa-Rivera, MA

Thank you, and we have a lot of folks on that are in their 80s, 70s and wondering if there is a certain age that they are not able to participate in a clinical trial at this time.

Matthew Lunning, DO

So, I think that you can find many trials which are trying to define a population by age, and I think that age may be one of the criteria, but often they're trying to define a population that may not be able to get a type of therapy that is considered more intensive. Okay, and so, then based upon some of the criteria, if your age let's say greater than 70. I can give another example of a trial called the PILOT trial where those were trying to define a population that was called transplant not eligible, and this was for patients with diffuse large B-cell lymphoma.

And one of the criteria was age over the age of 70, but they also looked at other criteria that somebody under the age of 70 may be eligible for, such as compromised kidney function, compromised lung function, compromised heart function. Okay, and each one of those, if they met still criteria, could go onto the trial; but trying to test a population that would be considered noneligible by some form of certain definitions for a bone marrow transplant using their own cells called an autologous stem cell transplant.

So, I think that you can find studies which won't have an upper age limit or you will find studies that will define 70 or older as one of the criteria for the trial. So, I think that that's, really, one of the things that we're trying to really think hard about as we bring trials to represent, to different populations.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience please.

Donna, calling from Texas

Yes, I'd like to know the signs of lymphoma and just make a short message. My husband died in 2020 with large B lymphoma, and he'd been coughing for five years, been going to an oncologist. They did bloodwork but nothing came up. They did not do any other testing. Well he died within two weeks when he went in September of 2020, and they didn't know what type of lymphoma it was. And my concern is how do you find out, if it's not through the blood test, if they've got lymphoma because he was spitting up white phlegm for five years; and they could not find anything.

Matthew Lunning, DO

Well, thank you, Donna, for your question. And so, speaking to signs and symptoms of lymphoma, you know, lymphoma is an immune system disorder; and so, many times bloodwork may show that there's an abnormality that leads you to doing other testing. And sometimes there may not be any abnormalities on blood tests. Often, lymphoma can arise in the lymph nodes; and lymph nodes are kind of glands that live in certain areas where you can palpate by your hands. And we're supposed to have lymph nodes, and they're supposed to be about one centimeter in size. I often give centimeters, but I'd say like a jelly bean in size.

And these can live in your neck, they can live underneath of your arms, they can live in your inguinal region where you can potentially palpate them; or they live kind of in the middle of the chest or in the middle of the abdomen where you can't always easily feel them, and you can only see them if I put on my radiation glasses or do things like CAT (computerized tomography) scans or chest x-rays perhaps if it was an older way to find larger masses or CAT scans of the abdomen and pelvis.

Sometimes other symptoms of lymphoma may be drenching night sweats. Drenching night sweats is where it's almost like somebody poured a bucked of water over you, you're changing your sheet. So, you're changing your shirt. Fevers can be a symptom of lymphoma. And then unintentional weight loss. So, unintentional weight loss is where you don't intend to lose weight, and you just can't keep the pounds on.

Now these are called our B symptoms, and B symptoms may be present, and they're more commonly present in our aggressive lymphomas. But sometimes our slow-growing lymphomas, okay, may be diagnosed incidentally. Somebody notices an abnormality, and a white blood cell count being elevated and may find a diagnosis of a lymphoma. Or you may find an incidental, abnormal size lymph node on a test for something else like a CAT scan for a person who has a smoking history that meets criteria for surveillance CAT scans to ensure that there is no lung cancer. You know, you may find an abnormal axillary lymph node or a lymph node under the arm, which is then biopsied and found to be lymphoma. So, many different ways, but sometimes lymphoma can be asymptomatic also or have no symptoms.

Lizette Figueroa-Rivera, MA

Thank you. And Donna, we do have the support services for you here at The Leukemia & Lymphoma Society; and I'll be giving out our number for our Information Specialists after the Question-and-Answer period.

Doctor, a lot of folks are asking about the financials associated with clinical trials. AJ is asking, "Who funds the clinical trials?"

Matthew Lunning, DO

There's many different ways that clinical trials are funded. The first way that I'll discuss is what's called a federal funded mechanism. This is through the National Cancer Institute (NCI), and often this can be done in smaller, multicentered clinical trials or they go through what's called cooperative group mechanisms; and these are large groups with multiple institutions and trials kind of are raised up, are discussed, voted on. The idea is felt to be a good idea, and a clinical trial goes forward to multiple institutions and are funded often through the National Cancer Institute mechanism.

Another way that clinical trials are funded are through an industry mechanism. So, this would be a company that has a compound or a drug that they think is going to be effective in a disease like lymphoma. And in those industry-sponsored clinical trials, the sponsor negotiates individually with the center, like a cancer center in your region, to provide access to that clinical trial through, in contracting and work with a partner.

The third is what's called an investigator-initiated trial. Often these are single site or single center and perhaps multicenter, and this is where an investigator at their own institution may have a question or an answer and may ask for access to a study drug that's either approved or not approved from an industry partner or from the National Cancer Institute through different mechanisms and provides that clinical trial just at an individual site. So, many different ways that clinical trials are funded through many different mechanisms.

Many times, these fundings can come through grants given by societies to help support the conduct of clinical trials, and so, we are looking for different, many different ways to fund these trials.

Lizette Figueroa-Rivera, MA

Sure. And now people are asking how much does a patient have to pay for their clinical trial?

Matthew Lunning, DO

I think that's a very important question because part of the informed consent process should discuss a part of what is considered standard of care and, therefore, can be sent to your insurance for potential payment. And then there will be those items which are called resource nonbillable or felt to be only done for the aspect of research. And often those tests or those events are paid for by the sponsor of the research or through other mechanisms.

You know, so, certain parts of your clinical trial will and can be sent to your insurer, whether or not it's a third-party payer or it's something like Medicare or Medicaid. And so really, I think that's an important question that should be asked; and, you know, there are different financial support mechanisms to help get those answers.

Lizette Figueroa-Rivera, MA

Yes, definitely. There are a lot of resources out there for financial assistance. I know that George, that is also on the line, was contacted for a clinical trial but told that he needed to pay about $600,000 to be admitted. That doesn't happen often, does it, or how can people get assistance for that?

Matthew Lunning, DO

Often, you know, in clinical trials the experimental agent is often provided for whereas the clinical care that goes with that may be billable to an insurer. I think that there, to give that specific example, I'd have to have more detail into what and why from that standpoint.

Lizette Figueroa-Rivera, MA

Right, because there also can be folks that are looking at clinical trials that do not have insurance, correct?

Matthew Lunning, DO

Yes, if you're a patient and you don't have insurance and looking for clinical trials, that can be where there can be out-of-pocket costs.

Lizette Figueroa-Rivera, MA
Sure, and definitely the treatment center as well as The Leukemia & Lymphoma Society can try to find different resources to assist you with those costs.

We'll take the next question from the telephone audience please.

Virginia from Michigan

Yes, I was wondering if there is a way that I could notify my doctor to recommend a clinical trial for me. I am 82 years old, and I don't know if that would be possible.

Matthew Lunning, DO

Thank you, Virginia, for your question. The best way is to ask your doctor whether or not there are any resources or clinical trials available for me, whether or not at that facility or in a facility nearby. I think that one of the things that I think could be helpful is empowering through The Leukemia & Lymphoma Society or other tools to look. If you know your diagnosis, look for clinical trials in your region and perhaps bring those clinical trials or an example of that to just start the conversation at your next visit.

Lizette Figueroa-Rivera, MA

Thank you for the question. Our next question comes from Tommy. Tommy's asking, "Do clinical trials have to be done in the hospital or can they be done outpatient?"

Matthew Lunning, DO

Many of our clinical trials are done as an outpatient. The specific clinical trials from a safety standpoint may be asked to be done in the hospital or at least conducted in the hospital for a period of time. That should be very clear and spelled out in the informed consent about what is expected to be done outpatient and what is expected to be inpatient from that standpoint.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from our telephone audience please.

Alberta from South Dakota

Yes, how long will we be having those night sweats? Will they subside or will they continue?

Matthew Lunning, DO

Thank you, Alberta. So, night sweats are often a manifestation of the lymphoma, and so, if the lymphoma is being treated effectively, the night sweats should subside over time. If the night sweats are persisting but the lymphoma is getting better, then I think your doctor will often be asking if the night sweats are due to another concurrent condition and may be looking to assess for that.

But the night sweats, night sweats are very hard because night sweats are common in the change of the seasons. But when you're seeing them, that are drenching and they're soaking your shirt, soaking your sheets, they can be very annoying. And they usually come with other systemic manifestations or symptoms too that just make people not feel well. But, you know, the night sweats, the hope is when you're treating a disorder that's causing night sweats that the treatment in itself by treating the disease will help eradicate those pesky night sweats.

Lizette Figueroa-Rivera, MA

Thank you. Our next question from Jacqueline, she's asking, "If I'm on monthly maintenance, can I also be part of a clinical trial?"

Matthew Lunning, DO

So, it depends upon what the question of the clinical trial is. You know, there are many different kinds of clinical trials. Typically if you're on a therapy at that time, many clinical trials don't often allow concurrent treatment. But, again, different trials may be asking different questions; and so, I don't

think that it is ever a bad idea to ask that or entertain that because if it's a completely different question looking at a different aspect, then it may be appropriate or you may be eligible for that clinical trial.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from our telephone audience.

Erline from Michigan

Yes, this talks the age, upper age already; and my question is I just turned 80, and will I still be able to continue in the trial program? I am very concerned about the side effects of kidney and liver and others that comes along with it and I am bothered a lot with the neuropathy.

Matthew Lunning, DO

Yes, both within clinical trials and outside of clinical trials, we are very cognizant of the toxicity profile of the drugs that we do use, not only in heme malignancies but in oncology in general. And, you know, I think part of our job as oncologists is to judge the risk and the benefits of the therapies that we are using, both inside the clinical trial and outside of a clinical trial. It's why we still may, outside of a clinical trial, may hold therapies, dose reduce therapies for toxicities that we feel are related to those therapies or that are from antecedent or comorbidities that predate the therapy that may be either worsening slowly based upon time or with the combination of the therapy.

In a clinical trial, yes. You know, that's why there are certain eligibility criteria because certain drugs are metabolized or broken down by the kidneys and the liver, and so, that's why you have to have certain function eligibility of the kidneys, liver, other aspects of the body, whether or not it's lungs or heart may exclude you from a clinical trial because it's felt by the clinical trial at that time that excluding participants with those conditions presents a situation where the potential risks outweigh the potential benefits.

Lizette Figueroa-Rivera, MA

Thank you for the question. Our next question comes from Lisa. Lisa's asking, "Are placebos still used? I saw a slide on *clinicaltrials.gov* stating placebos are no longer used for cancer trials. Can you clarify?"

Matthew Lunning, DO

So, in the setting of a clinical trial, I can see a situation if you're getting the standard of care drug combination, and it's X plus standard of care, and the experimental arm is Y plus standard of care, if you wanted to know in a double-blinded fashion what the outcome or the contribution of that experimental agent is, then a placebo could be used in addition to the standard-of-care arm to relieve bias or try to lessen bias based upon safety profile, so on and so forth, so, from the standpoint of the investigator and from the participant.

But I think it would only be introduced as a placebo, placebo could only be introduced if it was being introduced in addition, you know, in combination with the standard-of-care agent in the control arm. And that's, again, to try and reduce bias in that randomized, clinical trial.

What I think people are hearing about is placebos where you're giving placebo to a patient with cancer, and you would expect in that situation for the cancer to grow as it would otherwise. And, you know, so those situations, there are lessor and lessor examples over time where placebo is an arm in a multiple-arm trial if the intent is a therapeutic intent.

Lizette Figueroa-Rivera, MA

Thank you. And Barbara is asking, "If a patient doesn't have a caregiver or doesn't live near a cancer research center, is participating in a clinical trial still possible?"

Matthew Lunning, DO

I think so. I think that part of the aspects of caregivers and logistics around clinical research is often getting to the center of interest initially. And once you're at the center of interest, some centers may have resources that can help support you getting back and forth to a center.

You know, in some clinical trials, there may be support offered within the clinical trials. As long as it's given and offered to everybody, may be able to support travel reimbursement; and that's really part of the informed consent and part of the discussion of the conduct of the clinical trial. So, it's kind of two-fold answer there, both one that is outside of clinical trials where there may be resources available to you at the center of interest. And part of it is that in some ways you don't know, and they often can't support if they haven't seen you as a patient.

Lizette Figueroa-Rivera, MA

Thank you. And Jim is asking, "What typically happens to trial participants when a drug gets FDA approval? Does the drug company continue providing it to participants who took a risk entering the trial or do patients then have to pay for this treatment?"

Matthew Lunning, DO

Yeah, I think that's a great question. I think some handle it differently where the drug may be continued to be offered to the subjects for continued follow-up, and sometimes there's a rollover to commercial product from that standpoint if you are on the clinical trial; and that's often discussed by the investigating team kind of at that time. And it's typically guided by the sponsor of the trial.

Lizette Figueroa-Rivera, MA

Thank you. And Laura is asking, "Typically, how long do clinical trials last? Is it more like months or years?"

Matthew Lunning, DO

Clinical trials can be very different. There can be, and it really depends upon what are the endpoints of the trial. For instance, a shorter clinical trial would be those patients who got three months of therapy, and at six months how many of them were in a complete response versus looking at randomized trial where the primary endpoint is overall survival. You know, that can be a trial that you're being followed for many years. There can be technologies like cellular therapy that are mandated to follow you for 15 years in one form or fashion after receiving a cellular therapy product.

So, you know, in that regards, the informed consent should help explain for how long you would be followed, whether or not you're in remission, or if the therapy doesn't work and there's evidence of progression, then how long you're followed after that event.

Lizette Figueroa-Rivera, MA

Thank you. And Jacob is asking, "How will the trial affect my daily life? Will I need to go to the clinic more often?"

Matthew Lunning, DO

That is a potential that within clinical trials there could be extra visits, there could be extra tests than would otherwise be done outside of a clinical trial. And that's why I think it's important as part of the informed consent process to ask what are more visits that you would see outside of what you would otherwise do when you're discussing with the investigator and the investigator team? What are my alternatives?

And I think that's important to help understand how this will be impactful to your day to day, and sometimes that just makes it such that the clinical trial just isn't the right fit for you. It's not the right therapeutic chair to sit in, and sometimes those visits may be reasonable; and you're willing to give up that time in your life to do those extra visits. And then there may be clinical trials where everything is done as it would have been done outside of a clinical trial. So, without asking those questions, it's hard to know. But I think that's a great question, as you're discussing clinical trial participation with your care team, that's a great question to ask.

Lizette Figueroa-Rivera, MA

Thank you. And Camille is asking, "If I've already participated in a CAR T trial and the cancer were to come back, could I then try another trial?"

Matthew Lunning, DO

So, that would come down to eligibility criteria and exclusion criteria. Some clinical trials have excluded patients who have received prior CAR T-cells; and some trials are, you know, looking as part of the eligibility that you may have had to have had CAR T-cell. And so, I think that expands the

spectrum right now, and the eligibilities are everchanging as we see populations and therapies evolve over time. So, I would not say that just because you had an experimental CAR T-cell in a clinical trial, that means that all of the clinical trial options for you are exhausted. I would not say that.

Lizette Figueroa-Rivera, MA

Thank you. And Scott is asking, "We are currently in a trial. What information can we expect from how the others on the trial are doing?"

Matthew Lunning, DO

Yes. So, you know, often we don't have that level of ability to kind of comment on how the ten patients are doing and you're patient eight. You know, and the other nine are doing like this. There may be updates of the data as the trials are ongoing at international or national conferences. Often if that's the case, you know, one of the things that you could ask is has my trial been presented that you're participating in; and what were the outcomes of that report? And I think that you can ask that to your care team and see what answer they would give you.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Betsy. Betsy's asking, "I keep hearing 'bed to bench side' and how it takes more than ten years to get a drug approved. Does it always take this long to approve a drug?"

Matthew Lunning, DO

Well, we saw during the pandemic that it didn't take very long to get vaccines approved, so really, I think a lot of times it depends upon the disease, how crowded the space is from a known therapeutic. You know, it depends upon the activity of the drug; and so, there's a lot of variables that go into play once the drug enters into kind of your Phase I/II/III process. I think that really streamlining clinical trial design has been a major effort over the last decade. You know, we've seen examples of what are called seamless design, Phase I clinical trials.

You know, I stated very dogmatically in one of my slides, Phase I clinical trials are very low accruing patients. But then we have examples of clinical trials with seamless Phase I design where I becomes II, and you see reports of hundreds of patients leading to an approval of therapies within a said disease because you are able to go very quickly through that process of identifying a safe dose, identifying a target for a complete response rate, overall response rate, and then thirdly enough, durability to state that this therapy is providing significant benefit over what is currently available in that available space of the disease. So, whether or not it's frontline, second-line therapy, third-line or third line and beyond. So, it's really a lot of caveats that go into that.

Yes, it is true that there is a lot of time spent investigating not only the efficacy but the safety of drugs before they ever get into a Phase I clinical trial. That is often measured in many, many years also.

Lizette Figueroa-Rivera, MA

Thank you. And I've gotten a few questions in regard to this topic. Some participants are asking, "Can you enter a clinical trial without your oncologist's approval?"

Matthew Lunning, DO

I think often it will be your oncologist who will be talking to you about the clinical trial. If you're being treated at a center that doesn't have that clinical trial offered to them and you were to go to another center that has a potential clinical trial at that point, I think at that timepoint it behooves you and that care team to have a discussion about communication to an oncologist that doesn't have that clinical trial available because odds are there may be some necessary communication between the two groups to ensure that your care isn't affected and that there is communication both ways. So, to the root of the question, it's hard to know a clinical trial that would not necessarily go through the oncologist that's assisting you in your care.

Lizette Figueroa-Rivera, MA

Thank you.

Matthew Lunning, DO

The cancer-specific clinical trial.

Lizette Figueroa-Rivera, MA

Sure. And Barry's asking, "As you mentioned in the beginning about diversity with clinical trials, so, what efforts are being made to diversify the patient pool participating in clinical trials as it seems that we would want people of all ethnic backgrounds and rural patients participating in trials, not just those who live in or near the big cities or trial centers?"

Matthew Lunning, DO

I absolutely 100% agree that we should be looking at diversity as well as making sure that there is access, and we're lowering the barriers to clinical research, regardless of ZIP code, county, whether or not you're an urban county, a rural county, or a frontier county, which I have in my state of Nebraska. You know, we understand that there may be logistical barriers based upon distance from the treatment center.

But one of the ways we can get around and hopefully improve that is by dissemination of appropriate clinical trials to centers but also potentially having resources for those who are coming from a distance to participate in clinical research.

I think one of the other facets, if you look at diversity, is really going out and educating on the topic of clinical research. You know, clinical research is not a bad word or it's not two bad words. You know, it is how we move the field forward. It is how we have moved the field of oncology forward, and I think we can do better in the United States. And there's examples of countries that do it way better than the United States. And I think it comes down to kind of, speaking in my opinion, it comes down to the culture around clinical trials.

You know, and I think we can educate better, and we have done a significant amount to improve the safety and ethical nature of clinical trials in this country; and we will continue to do better. But I think we need to kind of have discussions about this, and this is a great start.

Lizette Figueroa-Rivera, MA

Well, thank you for that question, Barry, which was the last question today. And thank you all for all of your questions; and thank you, again, Dr. Lunning for your continued dedication to patients and for providing us with this update on clinical trials, giving us more hope for the future in treating blood cancers as more emerging therapies are being approved, so thank you.

Matthew Lunning, DO

My pleasure.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

And if we weren't able to get to your question today, you can call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time, or you can reach us by email at LLS.org/ContactUs. You may contact

our Clinical Trial Support Center by visiting our website at LLS.org/CTSC or LLS.org/Navigation. Again, LLS.org/CTSC or LLS.org/Navigation to learn more about the clinical trial process and to see if there is a clinical trial that may be right for you or your loved one.

LLS offers a variety of education and support resources, including online chats which are free live forums that are moderated by oncology social workers. We also offer free education videos and podcasts.

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer. For more information, you can visit LLS.org/Finances. And to order free materials, visit LLS.org/Booklets.

Please note that continuing education credit is not being offered for this program.

Thank you, again, Dr. Lunning for sharing your knowledge with us today and to everyone participating in today's program. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye, and we wish you well.

Matthew Lunning, DO

Have a great day.